Diagnosis and treatment of primary myelodysplastic syndromes in adults. Recommendations from the European LeukemiaNet

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Supplemental Methods

The development of these guidelines was a multistep process, consisting in:

1. Selection of an Expert Panel;
2. Systematic review of the literature and synthesis of evidence;
3. Key questions and list of indications;
4. Scenario analysis;
5. Formulation of recommendations.

1. Selection of an Expert Panel

Within the MDS work-package of the European LeukemiaNet, an Expert Panel was selected according to the framework elements of the NIH Consensus Development Program,[1] comprising physicians experienced in MDS and active in both care of patients and clinical research, with specific areas of expertise. During the first panel meeting, the Expert Panel agreed on the goal of the project: “to provide clinical practice recommendations that can support the diagnosis and the appropriate choice of therapeutic interventions in adult patients with primary MDS”.

2. Systematic review of the literature and synthesis of evidence

A systematic review of the literature has been performed according to the following criteria:

•English language;
•Year of publication: 1985-2012;

•Studies including 10 patients or more;
•Source: PubMed (1985-2012); proceedings of meetings of the American Society of Hematology, the European Hematology Association, the International Symposium on Myelodysplastic Syndromes and the American Society of Clinical Oncology (2002-2012);

An Advisory Committee was invited to perform a systematic review of the literature and to guide the consensus phases of developing the guidelines.

The level of evidence and the grades of recommendations were rated according to the Revised Grading System for Recommendations in Evidence Based Guidelines of the Scottish Intercollegiate Guidelines network Grading Review Group.[2]

3. Key questions and list of indications

The guidelines were developed based on a list of patient- and therapy-oriented questions. A list of key clinical questions clinical key-questions were generated and rank-ordered using the criterion of clinical relevance, pointing to the proper diagnostic procedures and the possible and recommendable strategies within each therapeutic category, to the possible and optimal patient subgroups, and to the risks deriving from the therapy.

The Expert Panel was invited to formulate evidence-based statements for each clinical question in an independent manner. Based on the statements of the experts for each question, the clinical variables will be defined that have to be taken into account in deciding whether to recommend a particular procedure (list of indications).

4. Scenario analysis

A scenario analysis is a procedure aimed at reaching a consensus on the indication of a certain treatment or procedure, in case scientific evidence is not at a level of detail sufficient enough to sustain everyday clinical decision. Therefore a method was defined that allows to combine the best available scientific evidence with the collective judgment by experts to yield a statement regarding the appropriateness of performing a procedure at

the level of patient-specific symptoms, medical history and test results (i.e. clinical scenario).

To this aim, a series of clinical scenarios were defined based on the parameters relevant to therapy choice. For each clinical scenario (i.e. patient case) the members of the Expert Panel were asked to grade the appropriateness of performing a certain procedure or providing a certain treatment according to a scale from 1 to 9, where 1 indicates that the questioned strategy is highly inappropriate, and 9 that it is highly appropriate.

A procedure or treatment is considered to be appropriate if "the expected health benefit (e.g., increased life expectancy, relief of pain, reduction in anxiety, improved functional capacity) exceeds the expected negative consequences (e.g., mortality, morbidity, anxiety, pain, time lost from work) by a sufficiently wide margin that the procedure is worth doing, exclusive of cost."[3] Although cost considerations are an important factor in deciding whether a procedure or treatment should ultimately be made available to patients, this discussion must include a broader group of individuals (physicians, consumers, payers), and has to take place once physicians have judged a treatment or procedure as effective. A cost-effectiveness analysis is outside the scope of this project, and should be committed to national working groups.

The appropriateness of providing a treatment or procedure is different from the necessity of performing it. The necessity is a more stringent criterion than appropriateness. A procedure is considered necessary when all the following criteria are met: (i) the procedure must be appropriate; (ii) it would be considered improper care not to provide this service; (iii) there is a reasonable chance that the procedure will benefit the patient (a procedure could be appropriate if it had a low likelihood of benefit but few risks; such procedure would not be necessary); (iv) the benefit to the patient is not small (a procedure could be appropriate if it had a minor but almost certain benefit, but it would not be necessary). Rating the necessity of providing a treatment is outside the scope of this analysis.

Then, an analysis of the panelists' scores was carried out (median, dispersion of ratings) with the aim at defining the level of agreement (agreement, indeterminate, disagreement) and the appropriateness rating (appropriate, uncertain, inappropriate).

5. Formulation of recommendations

Based on evidence from the literature, question-specific statements and scenario analysis final recommendations will be formulated. Three consensus conferences were held to reach a definite consensus.[4] Recommendations were formulated and ranked according to the supporting level of evidence. The level of Recommendation was graded according to the criteria of the Scottish Intercollegiate Guidelines Network Grading Review Group.[2]

References

1. The National Insitute of Health (NIH) Consensus Development Program (CDP).http://consensus.nih.gov.
2. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *Bmj*. 2001;323(7308):334-336.
3. Brook RH, Chassin MR, Fink A, Solomon DH, Kosecoff J, Park RE. A method for the detailed assessment of the appropriateness of medical technologies. *Int J Technol Assess Health Care*. 1986;2(1):53-63.
4. Delbecq A, van de Ven A, Gustafson D. Group techniques for program planning. A guide to nominal group and Delphi processes. Glenview, IL: Scott, Foresman and Co.; 1975.

Appendix 1 – List of key clinical questions

1. Which diagnostic procedures would you include in the work-up of patients with suspected MDS?
2. Which criteria should be used to classify MDS?
3. Which prognostic factors should be taken to decide therapeutic intervention?
4. Which criteria should be adopted to define response to treatment?
5. What variables should be taken into account for HLA typing?
6. Which patients are candidate to allogeneic stem cell transplantation?
7. Should a distinction be made between sibling donor transplantation and matched unrelated donor transplantation?
8. Which patients should be treated with intensive chemotherapy before transplantation?
9. What should be the best conditioning regimen taking into account which variables: stage of disease, age, comorbidity?
10. What should be the best source of stem cells?
11. Is there evidence that the outcome with auto-SCT is better than with AML-chemotherapy alone?
12. Is there evidence that auto-SCT similar or worse than with allo-SCT?
13. In which MDS patients would you consider autologous stem cell transplantation?
14. Which patients without suitable donor are candidate for intensive chemotherapy?
15. Which patients are candidate to post-remission chemotherapy?
16. What should be the best therapeutic regimen?
17. Which patients are candidate for low dose cytarabine?
18. Are there patients who clearly do not benefit from low dose cytarabine?
19. Which patients could benefit from therapy with hypomethylating agents?
20. What should be the best schedule of treatment with hypomethylating agents?
21. Which patients are candidate for immunosuppressive therapy?
22. Should a mainteinance immunosuppressive therapy be administered?
23. For which patients with MDS and anemia is treatment with erythropoietin with or without the addition of granulocyte-CSF indicated?
24. What is the best treatment schedule for erythropoietin with or without the addition of granulocyte-CSF?
25. Which patients with MDS should not be treated with hematopoietic growth factors?
26. What is the objective of RBC transfusion therapy?

27. What criteria should be used to decide the transfusion regimen?
28. Which consequences could be expected from iron overload?
29. Is there evidence in the context of MDS that iron chelation therapy is effective?
30. Which criteria should be used to administer platelet transfusion?
31. Should other approaches be considered in thrombocytopenic patients?

Appendix 2 – Synthesis of evidence and grade of recommendations

Treatment modality	*No. of studies*	*Highest level of evidence*	*Grade of recommendation*
Allogeneic stem cell transplantation	234	1-	B
• Remission induction therapy	121	2-	D
• Source of hematopoietic stem • cells	17	1-	D
Preparative regimen	169	2+	D
Remission induction chemotherapy	130	1-	B
Low dose chemotherapy	60	1-	B
Hypomethylating agents	150	1+	A
Hematopoietic growth factors	145	1+	A
Immunomodulatory drugs	58	1-	C
Iron Chelation Therapy	37	2+	D

Supplemental Table 1. Markers for flow cytometry analysis of dysplasia in MDS proposed by the International Flow Cytometry Working Group within the European Leukemia Network.*

General markers	***Erythroid lineage***	***Hematopoietic Progenitors***	***Maturing neutrophils***	***Monocyte lineage***
CD45	CD45	CD45	CD45	CD45
	CD71			
	CD235a			
CD34		CD34	CD34	CD34
CD117	CD117	CD117	CD117	CD117
HLA-DR		HLA-DR	HLA-DR	HLA-DR
CD11b		CD11b	CD11b	CD11b
CD13		CD13	CD13	CD13
CD16			CD16	CD16
CD33			CD33	CD33
CD14			CD14	CD14
	CD36			CD36
			CD64	CD64
CD7		CD7		
CD56		CD56	CD56	CD56
CD19		CD19		
		CD5		
				CD2
		CD15	CD15	
			CD10	

** Information is from Westers TM, Ireland R, Kern W, et al. Standardization of flow cytometry in myelodysplastic syndromes: a report from an international consortium and the European LeukemiaNet Working Group. Leukemia. 2012;26(7):1730-1741.*

Supplemental Table 2. WHO 2008 classification of MDS.*

Disease	Blood findings	Bone marrow findings
Refractory cytopenia with unilineage dysplasia (RCUD): refractory anemia (RA), refractory neutropenia (RN), refractory thrombocytopenia (RT)	Single lineage cytopenia, no or rare blasts (<1%), bicytopenia may be occasionally observed	Unilineage dysplasia (≥10% of the cells in one myeloid lineage) <5% blasts, <15% ring sideroblasts within erythroid precursors
Refractory anemia with ring sideroblasts (RARS)	Anemia, no blasts	Erythroid dysplasia only, < 5% blasts, ≥15% ringed sideroblasts within erythroid precursors
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia(s), no or rare blasts (<1%), no Auer roads, $<1x10^9$/L monocytes	Dysplasia in ≥ 10% of cells in 2 or more myeloid cell lineages, <5% blasts, no Auer roads (the percentage of ringed sideroblasts is irrelevant)
Refractory Anemia with Excess Blasts-1 (RAEB-1)	Cytopenia(s), <5% blasts, no Auer roads, $<1x10^9$/L monocytes (cases with Auer rods and <5% blasts in the peripheral blood and <10% blasts in the marrow should be classified as RAEB-2)	Unilineage or multilineage dysplasia, 5% to 9% blasts, no Auer roads (cases with Auer rods and <5% blasts in the peripheral blood and <10% blasts in the marrow should be classified as RAEB-2)
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenia(s), 5-19% blasts, occasional Auer roads, $<1x10^9$/L monocytes	Unilineage or multilineage dysplasia, 10% to 19% blasts, occasional Auer roads
Myelodysplastic syndrome, unclassified (MDS-U)	Cytopenias, no or rare blasts (≤1%)	Unequivocal dysplasia in less than 10% of cells in one or more myeloid cell lines when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS, <5% blasts *Cases of RCUD with pancytopenia *Cases of RCUD and RCMD with 1% myeloblasts in peripheral blood
Myelodysplastic syndrome associated with isolated del(5q)	Anemia, normal to increased platelet count, no or rare blasts (<1%)	Normal to increased megakaryocytes with hypolobated nuclei, <5% blasts, no Auer roads, isolated del(5q)

** Information is from Swerdlow et al. WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues, Fourth Edition IARC, Lyon, 2008.*

Supplemental Table 3. International Prognostic Scoring System (IPSS) for MDS.*

Variable	*Points*				
	0	*0.5*	*1*	*1.5*	*2*
Marrow blasts (%)	<5	5-10		11-20	21-30
Karyotype†	Good	Intermediate	Poor		
Cytopenias‡	0 or 1	2 or 3			

IPSS risk group	*Score*
Low	0
Intermediate 1	0.5-1.0
Intermediate 2	1.5-2.0
High	2.5-3.5

** Information is from Greenberg et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89(6):2079-2088.*

† Good: normal, del(5q) only, del(20q) only, –Y only; Poor: very complex (>2) abnormalities, chromosome 7 anomalies; Intermediate: other abnormalities.

‡ Cytopenias: hemoglobin <10 g/dL, neutrophil count < 1.5 x 10^9/L, platelet count < 100 x 10^9/L.

Supplemental Table 4. WHO classification–based Prognostic Scoring System (WPSS) for MDS.*

Variable	*Points*			
	0	*1*	*2*	*3*
WHO category	RA, RARS, MDS with isolated deletion (5q)	RCMD	RAEB-1	RAEB-2
Karyotype†	Good	Intermediate	Poor	-
Severe anemia (Hb <9 g/dL in males or <8 g/dL in females)	Absent	Present	-	-
Bone marrow fibrosis‡	The presence of grade 2-3 bone marrow fibrosis involves a shift to a one-step more advanced risk group after accounting for WHO category, karyotype, and transfusion requirement.			

WPSS risk group	*Score*
Very low	0
Low	1
Intermediate	2
High	3-4
Very high	5-6

** Information is from Cazzola M, Malcovati L. Prognostic classification and risk assessment in myelodysplastic syndromes. Hematol Oncol Clin North Am. 2010 Apr;24(2):459-68.*
† Good: normal, del(5q) only, del(20q) only, –Y only; Poor: complex (>2) abnormalities, chromosome 7 anomalies; Intermediate: other abnormalities.
‡ Bone marrow fibrosis should be evaluated according to the European consensus criteria.

Supplemental Table 5. Revised International Prognostic Scoring System (IPSS-R) for MDS.*

Variable	*Points*						
	0	*0.5*	*1*	*1.5*	*2*	*3*	*4*
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
BM Blast %	≤2		>2-<5%		5-10%	>10%	
Hemoglobin	≥10		8-<10	<8			
Platelets	≥100	50-<100	<50				
ANC	≥0.8	<0.8					

Cytogenetic risk group	*Cytogenetic abnormalities*
Very Good	-Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities
Very Poor	Complex: >3 abnormalities

IPSS-R risk group	*Score*
Very Low	≤1.5
Low	>1.5-3
Intermediate	>3-4.5
High	>4.5-6
Very High	>6

** Information is from Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012;120(12):2454-2465.*

Supplemental Table 6. International Working Group response criteria for MDS.*

Category	Response criteria
Complete remission†	Bone marrow: ≤5% myeloblasts with normal maturation of all cell lineages Peripheral blood: ▪ Hemoglobin ≥11 g/dL ▪ Platelets ≥100x10^9/L ▪ Neutrophils ≥1.0x10^9/L ▪ Blasts 0%
Partial remission†	All complete remission criteria if abnormal before treatment except: • Bone marrow blasts decreased by ≥ 50% over pretreatment but still >5% • Cellularity and morphology not relevant
Marrow complete remission†	Bone marrow: ≤ 5% myeloblasts and decrease by ≥50% over pretreatment Peripheral blood: if hematological improvement responses, they will be noted in addition to marrow complete remission
Stable disease	Failure to achieve at least partial remission, but no evidence of progression for > 8 weeks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following: ▪ Return to pretreatment bone marrow blast percentage ▪ Decrement of ≥50% from maximum response levels in granulocytes or platelets ▪ Reduction in hemoglobin concentration by ≥1.5 g/dL or transfusion dependence
Cytogenetic response†	Complete: disappearance of the chromosomal abnormality without appearance of new ones Partial: at least 50% reduction of the chromosomal abnormality
Disease progression	For patients with: ▪ Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts ▪ 5%-10% blasts: ≥ 50% increase to > 10% blasts ▪ 10%-20% blasts: ≥ 50% increase to > 20% blasts ▪ 20%-30% blasts: ≥ 50% increase to > 30% blasts Any of the following: ▪ At least 50% decrement from maximum response in granulocytes or platelets ▪ Reduction in hemoglobin by ≥ 2 g/dL ▪ Transfusion dependence ▪

Hematologic improvement:[‡]	
Erythroid response (pretreatment <11 g/dL)	Hemoglobin increase by ≥ 1.5 g/dL Relevant reduction of units of RBC transfused by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pretreatment transfusion number in the preceding 8 weeks. Only RBC transfusions given for a hemoglobin of ≤9.0 g/dL pretreatment will count in the RBC transfusion response evaluation
Platelet response (pretreatment<$100x10^9$/L)	Absolute increase of ≥$30x10^9$/L for patients starting with >$20x10^9$/L platelets Increase from <$20x10^9$/L to >$20x10^9$/L and by at least 100%
Neutrophil response (pretreatment <$1.0x10^9$/L)	At least 100% increase and an absolute increase >$0.5x10^9$/L
Progression/relapse after hematological improvement	At least one of the following: ▪ At least 50% decrement from maximum response levels in granulocytes or platelets ▪ Reduction in hemoglobin by ≥ 1.5 g/dL ▪ Transfusion dependence

** Information is from Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006;108(2):419-425.*

[†] *Responses must last at least 4 weeks*

[‡] *Responses must last at least 8 weeks. Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) ≥ 1 week apart.*